Original Paper

A Three-Day Octreotide-Containing Helicobacter pylori Eradication Therapy for Cure of Peptic Ulcers

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ABSTRACT

BACKGROUND/AIMS: Octreotide is used to arrest peptic ulcer hemorrhage. Since it has anti-secretory properties, it could also be used in *Helicobacter pylori* eradication therapy, to cure peptic ulcer before discharging patients from hospital. The aim of this pilot study was to determine safety and efficacy of an ultra short quadruple octreotide containing *H. pylori* eradication therapy in patients with peptic ulcer.

METHODOLOGY: Twenty-six consecutive symptomatic *H. pylori*-positive patients with duodenal (n=20) or gastric ulcer (n=6), were treated with a three-day course of octreotide 0.3 mg/day subcutaneously, amoxicillin plus metronidazole 2 g/day orally and colloid bismuth subcitrate 480 mg/day. CLO-test, culture and crush tissue smears were performed on admission to the study, at 4 and 8 weeks post treatment. The effect of octreotide on intragastric pH (n=10) was also investigated.

RESULTS: Octreotide significantly increased the mean 24-hour intragastric pH >3 over 68.9% of the time (37.1%-99.5%). There were no treatment side effects. Ulcer pain was abolished at between 2-12 days. By intention-to-treat 24/26(92.3%, 95% CI 82%-100%) ulcers had healed at 4 weeks. *H. pylori* eradication rate at 8 weeks was 88.5% (23/26) (95% CI 76%-100%).

CONCLUSIONS: Our ultra-short octreotide containing quadruple therapy is a safe and effective regime in eradicating *H. pylori* and healing peptic ulcers. It may be a suitable therapy for hospitalized patients with peptic ulcer hemorrhage.

INTRODUCTION

Somatostatin and octreotide(SMS 201-995) have been used in several trials to arrest peptic ulcer hemorrhage (1-3), with promising results. However, before discharging the patient from the hospital, cure of the peptic ulcer by *Helicobacter pylori* eradication therapy is desirable. Currently, effective anti-*H. pylori* treatment regimens include the classic (bismuth, metronidazole, tetracycline) and the newer (proton pump inhibitors (PPI) or H_2-blocker, amoxicillin, clarithromycin) triple therapies and quadruple (newer therapy plus Bismuth) therapy (4-7). These treatment schedules are given orally over a seven to 14-day period (5,6). In patients hospitalized for peptic ulcer hemorrhage and treated with octreotide, which has anti-secretory properties, the use of an ultra-short course of *H. pylori* eradication therapy may allow medication to be completed before the patients' discharge.

Therefore, the purpose of our study was to evaluate the safety, efficacy and tolerance of an ultra-short quadruple *H. pylori* eradication and peptic ulcer healing therapeutic regime, which includes octreotide. Because the effects of this therapy are not known, it has been decided to perform a pilot study in symptomatic patients with uncomplicated peptic ulcers.

METHODOLOGY

Patients

Twenty-six consecutive *H. pylori*-positive patients (18 males, 8 females, 51±9 years old) with symptomatic duodenal (n=20) or gastric (n=6) ulcer (≥5 mm) were invited to participate. They gave written consent to this prospective open study, after full explanation by the investigator. They had a history of peptic ulcer for a mean of 7.5±4.7 years, with one to three clinical recurrences per year. No patient had previous gastric surgery and had not taken non steroidal anti-inflammatory drugs, antibiotics or bismuth compounds for at least two months before the study. Women of child bearing age were excluded. The study protocol was approved by the Ethical Committee on Human Studies of the Department of Internal Medicine, Medical School of the Athens University according to the declaration of Helsinki.

Study Design

Upon entry to the study each patient had upper gastrointestinal endoscopy. All 26 patients were treated in hospital. They received a three-day course of octreotide (0.1 mg three times daily, subcutaneously), amoxicillin plus metronidazole (500 mg four times daily, orally) and colloid bismuth subcitrate (CBS) (240 mg twice daily). They were discharged on the morning of the 4th day and continued CBS treatment for four days. Daily symptoms were recorded on a symptom chart for ten days. Endoscopy was repeated at four and eight weeks post-treatment or earlier if symptoms recurred.

Detection of *Helicobacter pylori*

H. pylori infection was assessed by five antral biopsies used for culture (n=2), rapid urease test (CLO-test, Delta West Ltd, Bentley, W. Australia) (n=1) and crush biopsy smears (n=2) (8). The presence of serum antibodies (IgG) against *H. pylori* virulence factor CagA was also investigated by a commercially available *H. pylori* IgG Western blot (Autoimmun Diagnostika GmbH, Strasbourg, Germany). *H. pylori* infection was defined as a positive culture or a combination of both positive CLO-test and tissue smears. *H. pylori* eradication was evident by negative results of all three laboratory methods used at eight weeks post-treatment.

24-hour Gastric pH studies

The effect of octreotide treatment on 24-hour intragastric pH was measured in ten duodenal ulcer patients on the third day of octreotide treatment. Gastric pH monitoring was performed by placing the tip of a monocrystalant antimony catheter 10 cm below the lower esophageal sphincter. The electrode was connected to a portable pH recording device (Digitrapper III, Synectics Medical AB, Stockholm, Sweden). The recorded data was uploaded into the "EsopHogram Analysis Software" for analysis and review of the recording. Mean intragastric pH and percent time of gastric pH above 3 were calculated (9).

Statistical Analysis

Results are presented as mean±SD, median with ranges or percentages as appropriate. Clinical results were evaluated by chi-square test and proportions with both the "per protocol" and the "intention to treat" analysis. The former considers only the patients conducting the study and the latter includes all patients abandoning the study as treatment failures. The 95% confidence interval was also calculated (10).

RESULTS

Clinical and H. pylori Eradication Data

All patients had *H. pylori* colonization of the gastric mucosa on admission to the study. In addition, serum antibodies to CagA were detected in 20/26 (76.9%) patients (11). Compliance with therapy was excellent (26/26). No patient reported treatment side effects. They became asymptomatic at a mean of 5±3 days (range 2-12). In two patients ulcer pain recurred at four weeks. Endoscopy revealed that in both patients the duodenal ulcer had been reduced in size, but remained unhealed. They were still *H. pylori*-positive and withdrew from the study. Therefore, at four weeks in 24/26 patients the ulcer was healed and remained healed (24/26) at eight weeks (intention-to-treat: 92.3%, 95% CI 82%-100%). By an intention-to-treat analysis *H. pylori* eradication rate was 88.5% (95% CI 76%-100%) at eight weeks.

24-hour Gastric pH Studies

Mean 24-hour intragastric pH was 3.4±1.2 (3.2, 1.3-4.9, median with ranges). Gastric pH remained above 3 over 68.9±21.8 (68.6, 37.1-99.5, median with ranges) percent of the time. In five of the ten patients 24-hour intragastric pH was also studied at 4-8 weeks post-treatment. There were two technical failures of recording. The three successful pairs of recording were 49.2 vs 10.2, 55.7 vs 34.2, 67.7 vs 24.8 percent of time for gastric pH >3 for octreotide vs post-treatment period, respectively. All three post-treatment values were well outside the range of the values recorded during octreotide treatment periods.

TABLE 1. Results of Published Ultra-Short *H. pylori* Eradication and Ulcer Healing Regimens

	Course Duration	No of patients	Ulcer Healed at 4-8 Weeks	H.p. Eradication at 4-8 Weeks
B-S Sheu et al(12)	3 days[1]	25	-	16 (64%)
N.S. Kung et al(13)	2 days[2]	46	44 (95.7%)	35 (76.1%)
S.D. Ladas et al*	3 days[3]	26	24 (92.3%)	23 (88.5%)

* Present study.

[1] Omeprazole 80 mg/d + metronidazole 1.5 g/d + erythromycin 1.5 g/d (all given intravenously).

[2] Bismuth subcitrate 960 mg/d + tetracycline 2 g/d + metronidazole 1.6 g/d (Omeprazole 40 mg/d was given for a total of 7 days).

[3] Octreotide 0.3 mg/d + amoxicillin 2 g/d + metronidazole 2 g/d + CBS 480 mg/d.(CBS was given for a total 7 days.

DISCUSSION

Somatostatin and octreotide have been used in several trials and they have been effective in arresting peptic ulcer bleeding (1-3). In patients hospitalized for peptic ulcer hemorrhage that were treated with octreotide, a short course with antibiotics may be an effective therapy in eradicating *H. pylori* and cure the ulcer. This therapeutic approach has not been evaluated to date. We have therefore conducted this open prospective pilot study to evaluate safety and efficacy of an ultra-short octreotide-containing *H. pylori* eradication therapy.

The results of our study show that a three-day octreotide-containing quadruple *H. pylori* eradication therapy is effective to cure peptic ulcers. Two abstracts have recently been published using ultra-short (2-3 days) regimens in patients with non-actively bleeding duodenal ulcers. In the first study (12) *H. pylori*-positive patients with bleeding duodenal ulcers were treated by a three-day course of omeprazole plus two antibiotics, all given intravenously. The eradication rate at two months was 64%. In the second study (13) non-actively bleeding duodenal ulcer patients were treated with an oral two-day course of quadruple therapy. Per protocol ulcer healing was 96% and *H. pylori* eradication was 76% at five weeks (**Table 1**). In our study, ulcer healing rates were similar to those of Kung et al (13) ($x2=0.004$, $DF=1$, $p=0.95$) and *H. pylori* eradication rate was not significantly different ($x2=4.2$, $DF=2$, $p=0.12$) as compared with those of Sheu et al (12) and Kung et al (13) (**Table 1**).

Octreotide is known to have anti-secretory properties. It reduces gastric acid secretion by blocking the somatostatin receptors of parietal cells. This inhibitory effect on gastric secretions probably leads to a higher concentration of antibiotics and bismuth in the gastric mucosa and may increase the bactericidal potential of the antibiotics, which are more stable in a high pH environment. In most of our patients studied, the 24-hour intragastric pH was above 3 over 69% of time (17 hours/day). This increase of gastric pH has a favorable effect on ulcer healing (9).

There were problems with patient compliance due to the complex dose schedule and potential side effects of the seven or 14-day anti-*H. pylori* triple or quadruple eradication therapies. In one study eradication rate dropped from 96 to 69% for patients who took less than 60% of the regimen (14). To improve compliance, various modifications have been tested, such as the seven-day low-dose triple therapy, which has a 93.8% eradication rate at four weeks (15). Other modifications include the one-week low-dose anti-*H. pylori* therapy, which includes a PPI in combination with two antibiotics (16) and the four-day course of lansoprazole quadruple therapy (17). In our study compliance with therapy was excellent since the drugs were dispensed by nurses.

The results of the present open study have shown that an ultra-short (three-day) octreotide-containing *H. pylori* eradication quadruple therapy is safe. It is also highly effective to control ulcer pain, to eradicate *H. pylori* infection and heal peptic ulcers within four weeks. Since our regimen includes subcutaneous injections of octreotide, it is suitable for hospitalized patients because of peptic ulcer hemorrhage allowing medication to be completed before discharge.

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